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Perfluorooctane sulfonate: A review of human exposure, biomonitoring and the environmental forensics utility of its chirality and isomer distribution

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Abstract

Perfluorooctane sulfonate (PFOS) found extensive use for over 60 years up until its restriction in the early 2000s, culminating in its listing under the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2009. Efforts to minimise human body burdens are hindered by uncertainty over their precise origins. While diet appears the principal source for the majority of western populations, with other pathways like dust ingestion, drinking water, and inhalation also important contributors; the role played by exposure to PFOS-precursor compounds followed by *in vivo* metabolism to PFOS as the ultimate highly stable end-product is unclear. Such PFOS-precursor compounds include perfluorooctane sulfonamide derivatives, e.g. perfluorooctane sulfonamides (FOSAs) and sulfonamidoethanols (FOSEs). Understanding the indirect contribution of such precursors to human body burdens of PFOS is important as a significant contribution from this pathway would render the margin of safety between the current exposure limits and estimates of external exposure to PFOS alone, narrower than hitherto appreciated. Estimates derived from mathematical modelling studies,

put the contribution of so-called “precursor exposure” at between 10% and 40% of total PFOS body burdens. However, there are substantial uncertainties associated with such approaches. This paper reviews current understanding of human exposure to PFOS, with particular reference to recent research highlighting the potential of environmental forensics approaches based on the relative abundance and chiral signatures of branched chain PFOS isomers to provide definitive insights into the role played by “precursor exposure”.

Keywords

Perfluoroalkyl sulfonate, PFOS-precursors, perfluoroalkyl substances, biomonitoring, human exposure, chirality, isomer, body burdens

INTRODUCTION

Perfluoroalkyl substances (PFASs) are a family of synthetic compounds characterised by a fully fluorinated hydrophobic linear carbon chain, to which are attached different hydrophilic functional groups (Fromme et al., 2009). These chemicals have been manufactured since the late 1940s by 3M (3M, 1999) as well as other companies like Dupont, and have been produced and used in commercial products and industrial processes for over 60 years (Lindstrom et al., 2011). PFASs possess low molecular polarisability, short C–F bond length, and large C–F bond binding energy. Such characteristics govern the oil and water repellency, physical and chemical stability, and surfactant properties of PFASs (Zushi et al., 2012). These properties mean that PFASs have found wide use in a variety of applications, with historic production peaking at the end of the 20th century in North America and Europe (Paul et al., 2009). In an environmental context however, the strong C-F bond means that PFASs are resistant to thermal, chemical and biological degradation (Kissa, 2001) and are capable of bioaccumulation and long-range environmental transport, exemplified by their detection in the Arctic (Chaemfa et al., 2010; Sonne, 2010; Zhao et al., 2012). As a result, PFOS and its salts, as well as perfluorooctane sulfonyl fluoride (POSF) were in 2009 listed as persistent organic pollutants (POPs) under the Stockholm Convention (Geneva: Stockholm Convention Secretariat, 2009). POSF can degrade to PFOS directly or indirectly through chemical or enzymatic hydrolysis, and hence POSF-derived products can be degraded ultimately to PFOS (Zhao et al., 2012).

PFAS synthesis routes have been well described by Lehmler et al. (2005). The two main processes are electro-chemical fluorination (ECF) (3M, 1999), and telomerisation (Schultz et al., 2003), with PFOS, and PFOS salts synthesised via ECF. It is important to note here that a number of possible PFOS isomers exist in POSF based mixtures (in which process PFOS impurities are present between 0.1 and 5% (Paul et al., 2009) due to the nature of the ECF

process itself). The isomer composition of the commercial PFOS products can be up to 30% of total PFOS. Moreover, some of these isomers (specifically those that are branched chain) are chiral, with the result that the environmental fate and behaviour of PFOS may vary according to its isomeric and enantiomeric composition.

The main applications of PFOS and PFOS derivatives included uses in: inks, varnishes, waxes, fire-fighting foams, metal plating and cleaning products, coating formulations (for walls, furniture, carpeting, food packaging), lubricants, water and oil repellents for leather, paper and textiles (3M, 2000). Before 2003, POSF was used as a raw material for the synthesis of PFOS (among other perfluorooctane sulphonamide derivatives) (Burk et al., 2011). However, 3M Company replaced PFOS with perfluorobutane sulfonate (PFBS) after 2003, because the former was considered harmful to the environment (Renner, 2006).

Over the last 15 years, a substantial weight of evidence has emerged concerning environmental contamination with PFOS, consequent human exposure, and its effects. This paper reviews this evidence, and summarises recent developments that exploit the chirality and relative abundance of branched chain PFOS isomers to provide valuable insights into the environmental fate and behaviour of PFOS and its precursors.

SOURCES, PRODUCTION AND APPLICATIONS

The history of PFAS production is difficult to portray accurately due to the proprietary nature of this information (Lindstrom et al., 2011), but the 3M Company was the first main producer of POSF (an intermediate product for the synthesis of PFOS) with the total cumulative production estimated to be approximately 96,000 t in the peak years between 1970 and 2002 (Paul et al., 2009). In 2002, the 3M Company discontinued its production; however other companies commenced manufacture at this point to meet existing market demands, with an

estimated 1,000 t being produced annually since 2002 (Paul et al., 2009). In addition to the 3M production facilities in the USA, another 6 plants were located in Europe (4 in EU member states), 6 in Asia (of which 4 were in Japan) and one in South America (Paul et al., 2009).

The main way of synthesising PFASs is ECF. In this process, a straight chain hydrocarbon is reacted with H and F atoms and electricity to substitute all of the hydrogen atoms with fluorine (Kissa, 2001). This constitutes the main process of POSF synthesis, generating about 70% of the straight chain product with the remainder comprised of branched and cyclic isomers. POSF can then be used in a series of reactions via N-methyl and N-ethyl perfluorooctane sulfonamide (N-MeFOSA and N-EtFOSA) to yield N-methyl and N-ethyl perfluorooctane sulfonamidoethanols (N-MeFOSE and N-EtFOSE), which historically were used to produce polymeric materials and phosphate esters respectively, and used on surface coatings for textiles and paper products (Paul et al., 2009; Olsen et al., 2005, D'Eon and Mabury, 2011).

The major applications of POSF derivatives have been: (1) in carpets to impart stain and dirt repellence, (2) in apparel to provide water repellence, (3) in paper and packaging to afford oil and grease repellence, (4) in performance chemicals such as hydraulic fluids for aviation, and (5) in aqueous fire-fighting foams (AFFFs). AFFFs are perhaps the most prominent method of widespread environmental dispersal, with use for oil drilling and military fire-fighting practice (Paul et al., 2009).

All compounds produced from POSF are widely referred to as “PFOS equivalents” or just “PFOS”, due to their collective potential to degrade or transform into PFOS. In contrast, PFOS itself is extraordinarily stable in the environment, with no known natural mechanism of degradation. Hence, regulatory bodies have been working to reduce the production and use of some PFASs (Zushi et al., 2012). The 3M company, together with the US Environmental

Protection Agency (USEPA) resolved to decrease the production of PFOS and related compounds between 2000 and 2002 (3M, 2008). At the same time, Significant New Use Rules (SNUR) were also put in place (2000, 2002, and 2007) in the US, designed to restrict the production and use of materials that contained PFOS or its various precursors. The EPA then worked with eight leading chemical companies in the 2010-2015 PFOA Stewardship Program to reduce emissions and residual content of PFOA and long-chain PFCAs by 95% by 2010, with the long-term goal to work towards elimination of long-chain PFCAs by 2015 (USEPA, 2010).

Within the EU, PFOS and its derivatives are regulated on the market or only used as a substance or constituent of preparations listed as permissible in the EU Directive (2006). Under this directive, PFOS may still be used in applications that are deemed un-substitutable, including photolithographic processes, photographic coatings, mist suppressants for non-decorative hard chromium (VI), plating/wetting agents in controlled electroplating systems (pollution prevention and control are required), and hydraulic fluids for aviation. Such regulation started within the EU in June 2008 (Zushi et al., 2012).

The presence of PFOS in the environment has been attributed to two major sources: direct and indirect (Armitage et al., 2009; Prevedouros et al., 2006; Paul et al., 2009). Direct sources are derived from the manufacture and application of PFOS and POSF (Paul et al., 2009). By comparison, indirect sources are a consequence of chemical reaction impurities or breakdown of so-called precursors such as N-Me-FOSE and N-Et-FOSE. It has been estimated that 85% of indirect emissions occur via release from consumer products during use and disposal (3M, 2000).

HEALTH CONCERNS

General toxicological findings associated with laboratory animals exposed to PFOS include hepatomegaly and hepatic peroxisome proliferation, liver, testicular (Leydig cell), and pancreatic (acinar cell) tumours, reproductive and developmental deficits, neurotoxicity, and immunotoxicity (DeWitt et al., 2012).

Most of the reported studies concerning PFOS toxicity have been conducted on mice, with subsequent extrapolation to humans of observed murine effects complicated by interspecies variability in toxicokinetics. Even gender and ethnic origin can play a role (Kato et al., 2011). Adverse effects attributed to PFOS in rodents include decreased body weight, increased liver weight, and a steep dose-response curve for mortality (Seacat et al., 2003), as well as an increase in hepatocellular and follicular cell adenomas at high exposure levels (3M, 2002).

Human studies carried out on workers occupationally exposed to PFAS have generally yielded inconsistent results. While such workers have circulating blood levels of PFAS that are hundreds of times those of non-occupationally exposed individuals (Olsen et al., 2003; Steenland et al., 2010), it is difficult to determine conclusive results in these studies (either positive or negative) because sample populations are small, historical exposure levels are uncertain, individuals often have had simultaneous exposures to other compounds, and they may have pre-existing conditions that complicate evaluations (Fletcher et al., 2013). Compared to PFOS, studies of PFOA exposed workers are more numerous. Several studies have shown a positive association between PFOA exposure and cholesterol, which could have implications for the development of cardiovascular disease. PFOA has also been associated with elevated uric acid levels, which may in turn lead to hypertension and cerebrovascular disease (Lindstrom et al., 2011; Olsen et al., 2003; Costa et al., 2009; Sakr et al., 2007).

Based on the toxicological evidence available to date, chronic exposure guidelines are being developed for PFOS and PFOA by the USEPA and other jurisdictions for water and food, but

little has been done thus far for other PFASs. A review of current global guidelines and regulations can be found in Zushi et al. (2012), and some especially pertinent illustrative examples are discussed briefly here. The continuing uncertainty surrounding the human health impacts of PFASs is reflected in the disparity between the values promulgated by different jurisdictions. The risk from PFOS for human adults has been evaluated as low based on the Margin of Exposure (MOE), derived from the ratio of the provisional tolerable daily intakes (pTDI) and the level of intake (Zushi et al., 2012). Fromme et al. (2009) estimated the average (and high end) daily intake of PFOS and PFOA, including the indirect contribution from their precursors, as 1.6 (11.0) and 2.9 (12.7) ng/kg bw/day, respectively. These exposures are comfortably lower than the pTDIs for the general adult population of 100 ng/kg bw/day for PFOS and 3000 ng/kg bw/day for PFOA, promulgated by the German Federal Institute for Risk Assessment (BfR) and the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) respectively. Moreover, the USEPA issued provisional short-term health advisories for PFOS (200 ng/L) and PFOA (400 ng/L) in drinking water, on the assumption that short-term consumption below these levels will safeguard public health (USEPA, 2009).

In a parallel approach to limit values for external exposure via ingestion of food and water, the Biomonitoring Commission of the German Federal Environmental Agency used the 95th percentile concentration values of two German studies (Midasch et al., 2006; Fromme et al., 2007b), to establish reference values for PFOA and PFOS in plasma of children and adults. These reference values specify a maximum permissible presence of PFOS of 10 µg/L for children, 20 µg/L for adult females, and 25 µg/L for adult males (Wilhelm et al., 2009).

HUMAN EXPOSURE

The first report of the presence of PFOS, PFOA, and other PFASs in samples of human blood purchased from biological supply companies emerged in 2001 (Hansen et al., 2001), although the first paper regarding the presence of organofluorine compounds in biological samples dates from 1968 (Taves, 1968). Since then, a considerable database concerning human exposure to PFASs has emerged. The following section summarises current understanding of this topic with particular reference to PFOS.

Human Biomonitoring Data

With respect to human biomonitoring, concentrations of PFAS in human blood (whole blood, plasma and serum) in the general population have been reviewed recently (Angerer et al., 2011; Fromme et al., 2009) (*Table 1*). Most human biomonitoring studies are not carried out on whole blood, but on serum. The first reported concentrations of PFOS in blood were published by Hansen et al. (2001). This study showed 100% of the blood samples contained PFOS at concentrations ranging from 6.7 to 81.5 ng/mL. Following this seminal report, concern about how PFOS enters and remains in the human body increased, leading to the publication of a number of studies, each based on the analysis of a large number of blood samples. Amongst the most relevant of these are those of Calafat et al. and Kato et al. (Calafat et al., 2007a and 2007b; Kato et al., 2011) in the North American population, which each discuss results from the National Health and Nutrition Examination Surveys (NHANES) carried out by the US Center for Disease Control and Prevention, and published in the Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2009; CDC 2013). In these reports, the presence of a range of chemical contaminants is studied in blood and urine from the general population of the USA. The PFOS measurements reported in the two papers from Calafat et al. refer to the NHANES results from 1999-2000 and 2003-2004, and are based on 1,562 and 2,094 serum samples, with a detection frequency (DF) > 96% for PFOS in both studies, and geometric means of 21.1 and 20.7 ng/mL respectively. One of the

studies (Calafat et al., 2007b), also reported that geometric mean PFOS levels declined by 32% between 1999/2000 and 2003/2004. Moreover, the most recent (2007/2008) NHANES results (Kato et al., 2011), indicate that PFOS concentrations continue to decline (exemplified by a geometric mean of 13.2 ng/mL). This follows an earlier report (Olsen et al., 2007b) of a decrease on PFOS levels in human blood in the general American population, from a geometric mean of 33.1 ng/mL in samples collected in 2000, to 15.1 ng/mL in samples collected in 2005. A second study (Olsen et al., 2008) based on a large number of human blood samples (around 600), highlighted that the observed ~60% decline in PFOS was consistent with its elimination half-life and the time period since the phase-out of POSF by 3M in 2000-2002. Combined, these studies suggest that restrictions on the production and use of PFOS have led to reductions in human exposure in the US, although it remains in the environment, wildlife and the US population (CDC, 2009). Other US studies document similar PFOS concentrations in blood, but can not provide evidence of a temporal trend. Specifically, Hansen et al. (2001), as well as Olsen et al. (2005), published results in which median PFOS concentrations were 26.2 and 34.7 ng/mL for samples taken in the late 1990s/early 2000s (exact sampling dates not given) and 1974/1989 respectively. This apparent increase in human exposure in the immediate aftermath of the 2002 voluntary cessation of production by 3M, may be attributed to variation in the respective populations sampled in the two studies.

An important point is that – in line with Taniyasu et al., 2003 - the values in *Table 1* include data for both serum and whole blood. This approach is preferred here to the alternative format employed by others (e.g. Yeung et al. (2006) and Kannan et al. (2004)) whereby concentrations in whole blood were converted to concentrations in serum by multiplying whole blood concentrations by 2, to allow comparison across different studies. This conversion becomes even more sensitive when analysing PFOS precursors, due to their

different distribution between serum and blood (Martin et al., 2010). Notwithstanding the influence of serum versus whole blood basis concentrations, examination of the global database between 2004 and 2007, reveals some differences in both median and maximum PFOS concentrations in human blood recorded in different studies shown in *Table 1*. Likely causes of these between-study variations in the concentrations of PFOS include: international variations in use and exposure, as well as variations between sampled populations in lifestyle, age, ethnicity, and gender (Kato et al., 2011). While such differences in absolute concentrations of PFOS exist, they are not as marked as those observed for other halogenated persistent organic pollutants like polybrominated diphenyl ethers (Hites, 2004).

Table 2 reveals that, in addition to blood, human milk is being monitored increasingly. This shift towards monitoring milk may be attributed to its less invasive nature, greater sample availability and mass, recent improvements in the sensitivity and accuracy of ultra-trace analytical techniques (although these are likely still worse than for serum), and the dual role of human milk as an indicator of both the donor's body burden, and dietary intake of nursing infants. Of course, this is offset to some degree by the fact that human milk as a biomonitoring tool is restricted to a specific sector of the population. Moreover, comparing *Tables 1* and *2*, it is apparent that concentrations of PFOS in human blood exceed those in human milk. Several studies of human milk have been carried out since the first published reports. Most such studies show detection frequencies (DF) > 90%, except those of Bernsmann and Fürst (2008) (DF of 66% in Germany), and Guerranti et al. (2013), in which the detection frequency was below 50% (DF of 41% in Italy). Median concentrations range from 0.04 to 0.33 ng/mL, except for the study of Roosens et al. (2010) for the Flemish general population, who reported a median concentration an order of magnitude higher than other studies (2.9 ng/mL). Some of the samples reported by Roosens et al. (2010) were collected from donors living near a PFOS production facility, for which the authors also

reported high concentrations of PFOS in serum. Elevated concentrations of PFOS had also been reported previously in biota from the same location by Dauwe et al. (2007).

In contrast to blood and milk, only a small number of papers have reported concentrations of PFASs in other human matrices such as: liver, seminal plasma, and umbilical cord blood (Apelberg et al., 2007; Guruge et al., 2005; Inoue et al., 2004; Kärman et al., 2007a; Kuklenyik et al., 2004; Midasch et al., 2007; Olsen et al., 2003; So et al., 2006).

Scientific understanding of the origins of and influences on the presence of PFOS in humans is complicated by a number of factors (Lindstrom et al., 2011). Just as environmental degradation of PFOS precursors constitutes an important indirect source of PFOS contamination of the ambient environment; external exposure to PFOS precursors followed by *in vivo* metabolism, has been identified as a potentially substantial indirect contributor to human body burdens of PFOS (Trudel et al., 2008; Vestergren et al., 2008). Such indirect pathways are distinct from direct exposure via human contact with and uptake of PFOS itself. Moreover, PFOS (as well as other long chain PFASs) tend to accumulate in the human body with an estimated half-life of around 5 years (Olsen et al., 2007a). This slow elimination from the human body hampers efforts to determine how changes in lifestyle, diet, or other exposure-related factors influence blood levels. Notwithstanding this, while age has been suggested to exert little influence on circulating PFAS concentrations, with inconsistent results in cross-sectional studies (Haug et al., 2009; Harada et al., 2007), age associations could be consistent with dietary exposure in a post phase out situation (Nøst et al., 2014). However, as highlighted above, gender and ethnicity do seem to influence the accumulation of some compounds. In a recent paper, Kato et al. (2011) attributed differences in human body burdens between ethnic groups to ethnic differences in exposure related to lifestyle, the use of products containing PFASs, and diet. Meanwhile, gender-related differences in body burden (lower concentrations in women than men) have been attributed to physiological

differences (i.e. accumulation and elimination), as well as pregnancy, lactation and menstruation (Harada et al., 2004).

Direct Pathways of Human Exposure to PFOS

Non-occupational exposure to PFOS is thought to occur via the ingestion of food and drinking water, as well via inhalation and contact with indoor dust.

Drinking water. Data concerning concentrations of PFOS in drinking water are rather limited, and all published studies report concentrations in the ng/L range (see *Table 3*). Initially, Saito et al. (2004) reported PFOS concentrations in tap water from Japan to fall between 0.1 and 12.0 ng/L. Later studies (Lange et al., 2007; Ericson et al., 2009; Skutlarek et al., 2006; Tanaka et al., 2008) have reported higher concentrations however; up to 58 ng/L and 143 ng/L PFOS in tap water from Spain (Ericson et al., 2009) and Japan (Tanaka et al., 2008) respectively. Overall, PFOS is one of the most frequently detected PFASs (together with PFOA) in drinking water, with detection frequencies varying between 40 and 100% in published papers. Reassuringly, maximum values reported in drinking water to date, fall below the USEPA's short term advisory limit concentration for drinking water of 200 ng/L PFOS.

Indoor air and dust. In addition to drinking water; recent investigations show the indoor environment is a potentially important contributor to human exposure to PFASs including PFOS (D'Hollander et al., 2010; Fromme et al., 2009; Goosey and Harrad, 2011; Haug et al., 2011a). The first paper concerning PFOS contamination of indoor dust was published in 2003, by Moriwaki et al. (*Table 4*). Sixteen samples of house dust were analysed, containing concentrations of PFOS between 11 and 2,500 ng/g. Since then, similar studies have been carried out in Canada, Japan, Sweden, USA, Australia, the UK, and Spain, with wide

variation in concentrations found. While Bjorklund et al. (2009) reported concentrations of PFOS in dust from 10 houses in Sweden in 2009 to range between 15 and 120 ng/g, Strynar et al. (2008) and Kato et al. (2009) reported substantially higher concentrations, ranging between 8.9 and 12,100 ng/g in the USA, and 2.6 and 18,000 ng/g in Australia. Median concentrations further reflect international variations, being 38 ng/g for the Swedish study, and 201 ng/g and 480 ng/g for the Canadian and Australian surveys respectively. Moreover, Goosey and Harrad (2011) also reported statistically significant differences ($p < 0.05$) between concentrations of PFOS in dust from different countries. Specifically, UK, Australia, Canada, France, Germany, and US > Kazakhstan; and UK, Australia, Canada, and US > Thailand. They attributed such differences to lower use of products containing PFAS in Kazakhstan and Thailand compared to Europe, North America, and Australia.

Moreover, recent studies have reported concentrations of PFOS and other PFAS in indoor air (principally vapour phase, but with some particulate phase compounds incorporated) (Ericson Jogsten et al., 2012; Goosey and Harrad, 2012; Shoeib et al., 2011). In these, PFOS was the most prevalent PFAS, with a wide range of concentrations between countries (for example, lower values detected in Spain, higher in the UK). The frequency of detection for PFOS in indoor air is more variable than for dust (in air the range is from 0% to 100% c.f. 60% to 100% for dust).

Outdoor air. Outdoor air has also been studied, sometimes in conjunction with indoor air. Shoeib et al. (2005) reported PFAS concentrations in outdoor air were 1 or 2 orders of magnitude lower than in indoor air, as data from more recent studies in *Table 5* corroborate. This is consistent with the hypothesis that substantial indoor sources of PFOS exist, with the result that indoor air likely exerts an appreciable influence on outdoor atmospheric contamination. While this would logically lead to higher atmospheric concentrations of PFOS in conurbations due to higher urban building densities; Barber et al. (2007) reported higher

detection frequencies of PFAS (including PFOS) than expected in outdoor air from rural areas. Such findings suggest the environmental distribution of PFAS is complex, and that indoor environments are not the only driver influencing outdoor contamination.

Diet. Overall, based on the exposure models and reviews published to date (D'Eon and Mabury 2011; Ericson-Jogsten et al, 2012; Fromme et al., 2009; Trudel et al., 2008; Vestergren et al., 2008); food contaminated via bioaccumulation, has been suggested by several authors as the principal pathway of direct human exposure to PFOS; (D'Hollander et al., 2010; Fromme et al., 2007a; Trudel et al., 2008; Kärman et al., 2009; Vestergren et al., 2008; Fromme et al., 2009, Herzke et al., 2013).

In 2012, Ericson-Jogsten reported diet as the main pathway of PFOS exposure for adults and toddlers from Catalonia, Spain (constituting more than 70% of the daily total intake). Ingestion of water was identified as the second most important human exposure pathway, with inhalation of air and ingestion of dust considered negligible (< 0.5% of the total intake). An alternative Scenario-Based Risk Assessment approach (SceBRA) (Scheringer et al., 2001) was used in the studies of Trudel et al. (2008) and Vestergren et al. (2008). Both studies reported food ingestion as one of the most important pathways under three different exposure scenarios, although there was some divergence between the two studies about the absolute contribution of diet. Moreover, house dust ingestion was identified as a significant direct exposure pathway in both studies (though different absolute values of its proportional contribution to overall exposure were reported); while for some other pathways, e.g. direct hand contact with carpets treated with products containing PFOS and subsequent oral ingestion, assessment of their importance differs substantially between studies. Future evaluations of the relative contributions of different pathways to overall exposure to PFOS, will benefit from recent and on-going improvements in analytical techniques that permit detection of PFOS in foodstuffs and other exposure matrices at lower levels.

356

357 **Indirect sources of human exposure to PFOS**

358 As highlighted above, POSF-derived substances may be metabolised *in vivo* to PFOS,
359 constituting a substantial indirect source of human exposure to PFOS. The POSF-derived
360 substances in question represent a vast array of structures with the general formula
361 $C_8F_{17}SO_2NRR'$, that are referred to generically as “PFOS-precursors” (or “PreFOS” in some
362 literature, such as Asher et al., 2012). Consequently, as described by Prevedouros et al.
363 (2006), and Ross et al. (2012), two general routes of exposure may occur: (1) direct exposure
364 to PFOS, through diet, inhalation, and contact with contaminated settled dust (either by
365 ingestion or dermal contact), and (2) exposure to PFOS-precursors, followed by their
366 biotransformation in the body to PFOS. The main PFOS-precursor substances and its salts are
367 listed in *Table 6*.

368 PFOS-precursors are mainly degraded to PFOS by *in vivo* metabolic processes (Martin et al.,
369 2010; Xu et al., 2004). Some PFOS-precursors like N-Et-FOSA and N-Et-FOSE, have shown
370 low conversion factors < 1% in rats and trout (Xu et al., 2004; Tomy et al., 2004) or have not
371 yet been studied. However, in 2003, Seacat et al. reported a conversion factor to PFOS of up
372 to 20% in a study where rats were exposed long term to N-Et-FOSE; an observation
373 confirmed subsequently by Xie et al. (2009). Although the reported levels of PFOS-
374 precursors are generally lower and their physicochemical properties differ from those of
375 PFOS, a variety of them have been detected in water (Ahrens et al., 2009), in indoor and
376 outdoor air (Shoeib et al., 2005; Jahnke et al., 2007), in packaged food (Tittlemier et al.,
377 2006), and in live organisms (from mussels to bald eagles) and waterbird eggs (Kannan et al.,
378 2005; Wang et al., 2008). One of the most measured PFOS-precursors is
379 perfluorooctanesulfonamide (PFOSA), which is a stable intermediate in the pathway of
380 PFOS-precursor degradation to PFOS, and whose structure is depicted in *Fig. 1*.

Perfluorinated sulfonamide based products (PFSAm) are also important, as their production is associated with the presence of FOSAs and FOSEs as degradation or residual products. Positive correlations between the concentrations of PFOSA and PFOS have been found in biological samples (e.g. Martin et al., 2004) suggesting that PFOSA, and maybe other PFOS-precursors, can be important contributors to body burdens of PFOS in animal species (Asher et al., 2012).

As mentioned above, recent papers have examined the utility of human exposure models to evaluate the contribution of indirect exposure pathways to human body burdens of PFOS (Vestergren et al., 2008; D'Eon and Mabury 2011; Fromme et al., 2009; Gebbink et al., 2015). Such studies are still quite limited in number, but their general consensus is that the significance of indirect sources in driving human body burdens of PFOS should be taken into account, or even had hitherto been underestimated (e.g. D'Eon and Mabury (2011)). This becomes even more important in the wake of the 3M phase out, as while direct sources of PFOS exposure are expected to decrease in the general population, indirect sources stemming from continued use of PFOS-precursors remain. Vestergren et al. (2008) suggested the relative contributions of direct and indirect exposure were dependent on the level of exposure. While under low and intermediate exposure scenarios, direct dietary exposure appeared the principal pathway, intake of PFOS under a high-end exposure scenario was dominated by indirect precursor exposure via indoor dust (41-68%), and indoor air (10-19%). The study of Gebbink et al. (2015) considered comparable pathways of exposure to those studied by Vestergren et al. However, total exposure in the Gebbink et al study was 1-2 orders of magnitude lower, with indirect exposure to PFOS making higher and lower contributions to overall exposure under low (11%) and high (33%) exposure scenarios respectively than estimated previously. Gebbink et al. attributed the differences between their observations and those of previous studies, to their use of recent data reporting lower levels

of PFOS and PFOS-precursors in human diet (Ullah et al., 2014). However, other reasons such as the use of more recently published biotransformation factors describing the conversion of precursors, as well as the development of more sensitive analytical methods were identified as causes of the lower exposure estimates. Moreover, D'Eon and Mabury (2011) critically reviewed the contribution of PFOS precursors to observed body burdens of PFOS, and suggested that studies to date may underestimate the contribution of such indirect exposure. This was principally due to the fact that such studies consider indirect exposure to occur only as a result of exposure to PFOS precursors present as impurities or residual products from the manufacture of PFOS, but do not include exposure arising from manufacture and use of the precursors themselves.

In summary, studies to date suggest strongly that indirect exposure to PFOS makes an important contribution to human body burdens. However, such studies are not yet conclusive. For example, estimates of the contribution of such exposure varies between 10% and 70% of the daily intake of PFOS in the studies of Verstergren et al. (2008) and Gebbink et al. (2015) (based on the three different scenarios) and Fromme et al. (2009). Such variation is attributable to inherent uncertainties in pivotal parameters such as the estimated efficiency of precursor metabolism to PFOS. At the current time, efforts must focus on addressing: (1) the lack of data on the toxicokinetics of various PFOS-precursor compounds in animals, (2) the difficulty in extrapolating rodent data to humans, and (3) the fact that many commercially relevant PFOS precursors have yet to be determined in any sample (Martin et al., 2010). Overall, the uncertainties associated with studies to date, highlight a clear need for alternative approaches, and a small but growing number of studies suggests that exploitation of the chiral properties of some PFOS isomers and their precursors may constitute one such approach (Wang et al., 2009; Liu et al., 2015).

Isomer patterns and chirality of PFOS and its precursors – environmental forensic tools?

Historically, Σ PFOS has been quantified together (*see Tables 1 to 5*). Recently however, new approaches (discussed further below) have been suggested as biomarkers of exposure and applied in efforts to differentiate between direct exposure to PFOS and PFOS-precursor exposure (Benskin et al., 2009; Martin et al., 2010).

Isomer profiles. As described above, the processes via which PFOS precursors (i.e. POSF) are manufactured, are expected to produce about 70% of the linear isomer, with the remaining 30% made up of a mixture of various branched chain isomers. In contrast, due to preferential retention of linear PFOS in humans and rats, PFOS isomer profiles in animal species are expected to comprise <30% branched chain isomers. While this holds true for species such as fish and gulls for which $\geq 90\%$ of PFOS is the linear isomer (Asher et al., 2009; Gebbink and Letcher, 2010; Houde et al., 2008) (*Table 7*); in some human samples, the proportion of branched chain isomers can be 40-50% (Kärman et al., 2007b; Zhang et al., 2013; Beesoon et al., 2011, Liu et al., 2015). Moreover, an *in vitro* study using human microsomes has showed branched chain PFOSAs to be preferentially metabolised to PFOS relative to linear PFOSA (Benskin et al., 2009). This provides further evidence that precursor exposure may account for human PFOS isomer profiles that are enriched in branched chain isomers. This enriched profile in some human samples has been hypothesised as providing evidence of precursor exposure. Moreover, observed temporal and within-population variations in the relative abundance of branched chain PFOS isomers in humans (Kärman et al., 2007a; Haug et al., 2009), may be at least partly attributable to concomitant variations in precursor exposure. In fact, the study of temporal trends by Liu et al. (2015), shows the percentage of branched isomers in the Swedish population has increased from 32 to 45% between 1996 and 2010, suggesting that exposure to PFOS precursors is becoming more

important compared to direct exposure, as predicted by the theoretical models discussed earlier.

Current evidence to support this hypothesis is not clear-cut however (Ross et al, 2012). While excretion in rats of branched chain PFOSAs exceeded that of the linear isomer; a corresponding increase in the relative abundance of the sum of branched chain PFOS isomers was not observed in the same animals. More detailed analysis of the relative abundance of individual branched chain isomers in this study suggests a more complex situation. While the relative abundance in the studied rats of one branched isomer (5m-PFOS), increased relative to its abundance in a commercial PFOS mixture; that of another (1m-PFOS) decreased (Ross et al., 2012). This may point to a need to monitor relative abundances of individual branched chain isomers rather than the sum of all such isomers, to provide more conclusive insights into the relative contribution of precursor exposure. This conclusion is supported by the study of Gebbink et al. (2015), where an estimated isomeric pattern of 84% linear PFOS was calculated for exposure via water, diet, air and dust, that contrasts with isomer patterns observed in human serum samples (Beesoon et al., 2011; Haug et al., 2009; Benskin et al., 2007; Zhang et al., 2013). The potential feasibility of such a detailed isomer-specific approach is demonstrated by a study of PFOS isomer distributions in gull eggs from spatially distinct breeding colonies throughout the Laurentian Great Lakes (Gebbink and Letcher, 2010). In this study, 8 individual branched chain PFOS isomers were detected in gull eggs, with spatial variations in the contribution of linear PFOS in eggs highlighted as potentially at least partly attributable to location-specific variations in the PFOS precursor exposure.

Chirality. One feature of many PFOS isomers is chirality, including the environmentally relevant monomethyl-branched isomers 1m-, 3m-, 4m-, and 5m- PFOS, represented in *Fig. 2*, where “#m-” refers to the carbon position of the branched CF₃ group (Asher et al., 2012). Chirality has environmental significance for several reasons. The enantiomers of a chiral

481 compound rotate polarised light in opposite directions, but otherwise exhibit identical
482 physical and chemical properties. Consequently, environmental, physical, and chemical
483 processes generally affect both enantiomers identically (Kallenborn et al., 2001). However,
484 different enantiomers can interact differently with other chiral molecules (enzymes or
485 biological receptors), leading to different biological and toxicological behaviour (Hühnerfuss
486 et al., 2009). Moreover, unless production of a specific enantiomer is sought, the relative
487 abundance of each enantiomer, or the enantiomer fraction (EF), (referred to thereafter as the
488 chiral signature) is equal in commercially-produced chemicals. In such cases, the two
489 enantiomers (A and B) exist in identical proportions (*eq 1*) and the chiral signature is said to
490 be racemic ($EF = 0.5$). Consequently, observations of chiral signatures that deviate
491 significantly from racemic in environmental or biological matrices are strong evidence of
492 biodegradation or metabolism, and provide a powerful tool to enhance understanding of
493 environmental processes (Lehmle et al., 2010). Specifically, in the context of elucidating the
494 relative importance of precursor exposure, the EFs of chiral isomers such as 1m-PFOS in
495 freshly-manufactured PFOS are 0.5. In contrast, a branched chain PFOS precursor (1m-
496 PreFOS) was shown to be metabolised enantioselectively by human liver microsomes (Wang
497 et al., 2009). As a result, the observation of non-racemic EFs in human serum of 1m-PFOS,
498 combined with experimental evidence that 1m-PFOS itself is not excreted enantioselectively
499 in rats (Wang et al., 2011) (see *Table 7*); represents strong evidence of a discernible influence
500 of precursor exposure on human body burdens of PFOS. Recently, Liu et al. (2015) have also
501 found non-racemic EFs in serum samples from Swedish and US population, supporting
502 previous studies by Wang et al. (2009 and 2011). Furthermore, a significant correlation
503 between %br-PFOS (i.e. the proportion of Σ PFOS that are branched chain isomers) and 1m-
504 PFOS in samples from 1996-2000 has been also discussed there, but further studies are still

required in view of the fact that the observed changes in EF can explain only around 40% of the increment in branched isomers (Liu et al., 2015).

$$EF=A/(A+B) \quad (eq. 1)$$

The above are prime examples of how knowledge of chiral signatures of PFOS isomers in various environmental compartments including those pertinent to human exposure, offer potentially rich insights into various aspects of the environmental fate and behaviour of PFOS and its precursors. As well as helping elucidate the relative influence on human body burdens of direct exposure to PFOS compared to indirect exposure via metabolism of its precursors; studies of chiral organochlorine compounds indicate wider insights may also be possible. For example, measurement of the chiral signatures of polychlorinated biphenyls (PCBs) and organochlorine pesticides in relevant environmental matrices has enhanced understanding of issues such as: the relative contribution of primary versus secondary sources to outdoor air (Bidleman et al., 1998; Robson and Harrad, 2004), and the role of volatilisation from soil as a source of PCBs to grass (Desborough and Harrad, 2011). Moreover, tracking chiral signatures of PFOS and its precursors could lead to better understanding of toxicological effects on the human body, as enantioselective toxicity may exist (Loveless et al., 2006).

Forward look

PFOS is an environmental pollutant which has been widely studied. Significant manufacture of both PFOS and PFOS precursors continues today; e.g. PFOS production has increased in China since 2002 (with higher reported levels of PFOS in some regions of China than in the US, despite the small production volumes in China compared to reported 3M production

(Olsen et al., 2012)), while PFOS and PFOS-precursors are still being manufactured in Europe and Asia for certain applications (UNEP, 2010; Paul et al., 2009; Zhang et al., 2013). This review has highlighted the potential insights into its environmental fate that may be gained from better knowledge of the isomer and enantiomer-specific behaviour of both PFOS and its precursors. Despite this, at the current time, only a few papers have been published reporting the relative abundance of both linear and branched PFOS isomers in the environment. Even fewer papers have been published that address the chirality of PFOS and its precursors. In part, this is likely due to the fact that reference standards for branched chain isomers and individual enantiomers have only recently become available, and to the challenging nature of existing analytical methods for their measurement, exacerbated by the usually very low concentrations of individual branched chain isomers in environmental and biological samples. Moreover, as yet it has only proven possible to resolve the enantiomers of 1m-PFOS. As this represents only 2-3% of total PFOS and ~6-10% of Σ branched chain isomers (Riddell et al., 2009), there are inherent uncertainties in extrapolating findings for this one isomer to others. Furthermore, while variations in precursor exposure may explain variations in PFOS isomer profiles; other factors such as gender and pregnancy may also be influential. Despite these obstacles, exploiting the chirality and isomer patterns of PFOS and its precursors offers new opportunities to gain insights into their environmental fate and behaviour, as exemplified by previous studies of other chiral organohalogens like α -hexachlorocyclohexane and PCBs. Given the potential rewards, further development, validation, and carefully targeted application of analytical methods for the determination of chiral signatures of PFOS isomers are necessary. They will not be a trivial task; but they constitute urgent research priorities.

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REFERENCES

- 3M, 1999. The Science of Organic Fluorochemistry. Accessed September 2014
 - <http://www.fluoridealert.org/wp-content/pesticides/pfos.fr.final.docket.0006.pdf>
- 3M, 2000. Phase-Out Plan for POSF-Based Products. USEPA Docket ID OPPT-2002-0043. Accessed September 2014
 - <http://www.fluoridealert.org/wp-content/pesticides/3m.may16.2000.press.release.pdf>
- 3M, 2002. 104 Week Dietary Chronic Toxicity and Carcinogenicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS; T-6295) in Rats, Final Report. U.S. EPA Administrative Record, AR226-0956
- 3M, 2008. What is 3M Doing? Accessed September 2014
 - http://www.solutions.3m.com/wps/portal/3M/en_US/PFOS/PFOA/Information/Action/
- Ahrens L, Barber JL, Xie ZY, Ebinghaus R. Longitudinal and latitudinal distribution of perfluoroalkyl compounds in the surface water of the Atlantic Ocean. Environ Sci. Technol 2009;43:3122–3127
- Angerer J, Aylward LL, Hays SM, Heinzow B, Wilhelm M. Human biomonitoring assessment values: Approaches and data requirements. Int J Hyg Environ Health 2011;214:348–360
- Antignac JP, Veyrand B, Kadar H, Marchand P, Oleko A, Le Bizec B, Vandentorren S. Occurrence of perfluorinated alkylated substances in breast milk of French women and relation with socio-demographical and clinical parameters: Results of the ELFE pilot study. Chemosphere 2013;91:802–808
- Apelberg BJ, Witter FR, Herbstman JB, Calafat AM, Halden RU, Needham LL, Goldman LR. Cord serum concentrations of perfluorooctane sulfonate (PFOS) and

perfluorooctanoate (PFOA) in relation to weight and size at birth. (2007) *Environ Health Persp* 2007;115(11):1670-1676

- Armitage J, MacLeod M, Cousins IT. Modeling the global fate and transport of perfluorooctanoic acid (PFOA) and perfluorooctanoate (PFO) emitted from direct sources using a multispecies mass balance model. *Environ Sci Technol*. 2009;43:1134–1140

- Asher BJ, Wang Y, De Silva AO, Backus S, Muir DCG, Wong CS, Martin JW. Enantiospecific Perfluorooctane Sulfonate (PFOS) Analysis Reveals Evidence for the Source Contribution of PFOS-Precursors to the Lake Ontario Foodweb. *Environ Sci Technol* 2012;46:7653–7660

- Beesoon S, Webster GM, Shoeib M, Harner T, Benskin JP, Martin JW. Isomer profiles of perfluorochemicals in matched maternal, cord, and house dust samples: manufacturing sources and transplacental transfer. *Environ Health Perspect* 2011;119:1659–64

- Benskin JP, Bataineh M, Martin JW. Simultaneous characterization of perfluoroalkyl carboxylate, sulfonate, and sulfonamide isomers by liquid chromatography–tandem mass spectrometry. *Anal Chem* 2007;79:6455–64

- Benskin JP, Holt A, Martin JW. Isomer-specific biotransformation rates of a perfluorooctane sulfonate (PFOS)-precursor by cytochrome P450 isozymes and human liver microsomes. *Environ Sci Technol* 2009;43(22):8566–8572

- Barber JL, Berger U, Chaemfa C, Huber S, Jahnke A, Temme C, Jones KC. Analysis of per- and polyfluorinated alkyl substances in air samples from Northwest Europe. *J Environ Monit* 2007;9:530–41

- Bernsmann T, Fürst P. Determination of perfluorinated compounds in human milk. *Organohalogen Compd* 2008;70:718–721

- Bidleman TF, Jantunen LM, Harner T, Wiberg K, Wideman JL, Brice K, Su K, Falconer RL, Aigner EJ, Leone AD, Ridal JJ, Kerman B, Finizio A, Alegria H, Parkhurst WJ,

608 Szeto SY. Chiral pesticides as tracers of air-surface exchange. Environ Pollut
609 1998;102:43-49

610 • Björklund JA, Thuresson K, De Wit CA. Perfluoroalkyl compounds (PFCs) in indoor
611 dust: concentrations, human exposure estimates and sources. Environ Sci Technol
612 2009;43:2276–81

613 • Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, Jensen AA, Kannan,
614 K, Mabury SA, van Leeuwen SP. Perfluoroalkyl and polyfluoroalkyl substances in the
615 environment: terminology, classification, and origins. Integr Environ Assess
616 Manage.2011;7:513–541

617 • Calafat AM, Kuklenyik Z, Reidy JA, Caudill SP, Tully JS, Needham LL. Serum
618 concentrations of 11 polyfluoroalkyl compounds in the US population: data from the
619 National Health and Nutrition Examination Survey (NHANES) 1999–2000. Environ Sci
620 Technol 2007a;41:2237–2242

621 • Calafat AM, Wong LY, Kuklenyik Z, Reidy JA, Needham LL. Polyfluoroalkyl chemicals
622 in the U.S. Population: Data from the National Health and Nutrition Examination Survey
623 (NHANES) 2003-2004 and Comparisons with NHANES 1999-2000. Environ Health
624 Perspect 2007b;115(11):1596–1602

625 • Center for Disease Control and Prevention (CDC), 2009. U.S. Department of Health and
626 Human services. Fourth National Report on Human Exposure to Environmental
627 Chemicals. Accessed September 2014

628 ○ <http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf>

629 • Center for Disease Control and Prevention (CDC), 2013. U.S. Department of Health and
630 Human services. Fourth National Report on Human Exposure to Environmental
631 Chemicals. Updated tables September 2013. Accessed September 2014

632 ○ [http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Sep2013.p](http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Sep2013.pdf)
633 [df](http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Sep2013.pdf)

- 634 • Chaemfa C, Barber JL, Huber S, Breivik K, Jones KC. Screening for PFOS and PFOA in
635 European air using passive samplers. J Environ Monit 2010;12:1100–1109
- 636 • Costa G, Sartori S, Consonni D. Thirty years of medical surveillance in perfluooctanoic
637 acid production workers. J Occup Environ Med 2009;51(3):364–372
- 638 • Dauwe T, Van de Vijver K, De Coen W, Eens M. PFOS levels in the blood and liver of a
639 small insectivorous songbird near a fluorochemical plant. Environ Int 2007;33:357–361
- 640 • D'Eon JC, Mabury SA. Is Indirect Exposure a Significant Contributor to the Burden of
641 Perfluorinated Acids Observed in Humans? Environ Sci Technol 2011;45:7974–7984
- 642 • Desborough J, Harrad S. Chiral Signatures Show Volatilization from Soil Contributes to
643 Polychlorinated Biphenyls in Grass, Environl Sci Technol 2011;45:7354–7357
- 644 • DeWitt JC, Peden-Adams MM, Keller JM, Germolec DR. Immunotoxicity of
645 Perfluorinated Compounds: Recent Developments. J Toxicol Pathol 2012;40:300–311
- 646 • D'Hollander W, de Voogt P, de Coen W, Bervoets L. Perfluorinated substances in human
647 food and other sources of human exposure. Rev Environ Contam Toxicol 2010;208:179–
648 215
- 649 • Dreyer A, Ebinghaus R. Polyfluorinated compounds in ambient air from ship- and land
650 based measurements in northern Germany. Atmos Environ 2009;43:1527–35
- 651 • Ericson I, Gomez M, Nadal M, van Bavel B, Lindstrom G, Domingo JL. Perfluorinated
652 chemicals in blood of residents in Catalonia (Spain) in relation to age and gender: a pilot
653 study. Environ Int 2007;33:616–623
- 654 • Ericson I, Nadal M, van Bavel B, Lindström G, Domingo JL. Levels of
655 perfluorochemicals in water samples from Catalonia, Spain: is drinking water a
656 significant contribution to human exposure? Environ Sci Pollut Res 2008;15:614–619

- 657 • Ericson I, Domingo JL, Nadal M, Bigas E, Llebaria X, van Bavel B, Lindström G. Levels
658 of Perfluorinated Chemicals in Municipal Drinking Water from Catalonia, Spain: Public
659 Health Implications. *Arch Environ Contam Toxicol* 2009;57:631–638
- 660 • Ericson Jogsten I, Nadal M, van Bavel B, Lindström G, Domingo JL. Per- and
661 polyfluorinated compounds (PFCs) in house dust and indoor air in Catalonia, Spain:
662 implications for human exposure. *Environ Int* 2012;39:172–80.
- 663 • Fletcher T, Galloway TS, Melzer D, Holcroft P, Cipelli R, Luke C, Pilling LC, Mondal D,
664 Luster M, Harries LW. Associations between PFOA, PFOS and changes in the expression
665 of genes involved in cholesterol metabolism in humans. *Environ Int* 2013;57-58:2–10
- 666 • Fromme H, Schlummer M, Möller A, Gruber L, Wolz G, Ungewiss J, Bohmer S, Dekant,
667 W, Mayer R, Liebl B, Twardella D. Exposure of an adult population to perfluorinated
668 substances using duplicate diet portions and biomonitoring data. *Environ Sci Technol*
669 2007a;41:7928–7933
- 670 • Fromme H, Midasch O, Twardella Y, Angerer J, Boehmer S, Liebl B. Occurrence of
671 perfluorinated substances in an adult German population in southern Bavaria. *Int Arch*
672 *Occup Environ Health* 2007b;80:313–319
- 673 • Fromme H, Tittlemier SA, Völkel W, Wilhelm M, Twardella D. Perfluorinated
674 compounds - Exposure assessment for the general population in western countries. *Int J*
675 *Hyg Environ Health* 2009;212:239–270
- 676 • Fromme H, Mosch C, Morovitz M, Alba-Alejandre I, Boehmer S, Kiranoglu M, Faber F.,
677 Hannibal I, Genzel-Boroviczény O, Koletzko B, Völkel W. Pre- and Postnatal Exposure
678 to Perfluorinated Compounds (PFCs). *Environ Sci Technol* 2010;44:7123–7129
- 679 • Gebbink WA, Letcher RJ. Linear and branched perfluorooctane sulfonate isomer patterns
680 in herring gull eggs from colonial sites across the Laurentian Great Lakes. *Environ Sci*
681 *Technol* 2010;44(10):3739–3745

- 682 • Gebbink WA, Berger U, Cousins IT. Estimating human exposure to PFOS isomers and
 683 PFCA homologues: The relative importance of direct and indirect (precursor) exposure.
 684 Environ Int 2015; 74: 160-169
- 685 • Geneva: Stockholm Convention Secretariat, 2009. Governments Unite to Step-up
 686 Reduction on Global DDT Reliance and Add Nine New Chemicals Under International
 687 Treaty. Stockhlom Convention on Persistent Organic Pollutants (POPs). Accessed
 688 September 2014
 - 689 ○ <http://chm.pops.int/Convention/Pressrelease/COP4Geneva8May2009/tabid/542/language/en-US/Default.aspx>
- 691 • Genualdi S, Lee SC, Shoeib M, Gawor A, Ahrens L, Harner T. Global pilot study of
 692 legacy and emerging persistent organic pollutants using sorbent-impregnated
 693 polyurethane foam disk passive air samplers. Environ Sci Technol 2010;44:5534–9
- 694 • Goosey E, Harrad S. Perfluoroalkyl compounds in dust from Asian, Australian, European,
 695 and North American homes and UK cars, classrooms, and offices. Environ Int
 696 2011;37:86–92
- 697 • Goosey E, Harrad S. Perfluoroalkyl substances in UK indoor and outdoor air: Spatial and
 698 seasonal variation, and implications for human exposure. Environ Int 2012;45:86–90
- 699 • Guerranti C, Perra G, Corsolini S, Focardi SE. Pilot study on levels of perfluorooctane
 700 sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in selected foodstuffs and
 701 human milk from Italy. Food Chem 2013;140:197–203
- 702 • Guruge KS, Taniyasu S, Yamashita N, Wijeratna S, Mohotti KM, Seneviratne HR,
 703 Kannan K, Yamakana N, Miyazaki S. Perfluorinated organic compounds in human blood
 704 serum and seminal plasma: A study of urban and rural tea worker populations in Sri
 705 Lanka (2005) J Environ Monit 2005;7(4):371-377

- 706 • Hansen KJ, Clemen LA, Ellefson ME, Johnson HO. Compound-specific, quantitative
 707 characterization of organic fluorochemicals in biological matrices. *Environ Sci Technol*
 708 2001;35:766–770
- 709 • Harada K, Saito N, Inoue K, Yoshinaga T, Watanabe T, Sasaki S, Kamiyama S, Koizumi
 710 A. The influence of time, sex and geographic factors on levels of perfluorooctane
 711 sulfonate and perfluorooctanoate in human serum over the last 25 years. *J Occup Health*
 712 2004;46:141–147
- 713 • Harada K, Koizumi A, Saito N, Inoue K, Yoshinaga T, Date C, Fujii S, Hachiya N,
 714 Hirosawa I, Koda S, Kusaka Y, Murata K, Omae K, Shimbo S, Takenaka K, Takeshita T,
 715 Todoriki H, Wada Y, Watanabe T, Ikeda M. Historical and geographical aspects of the
 716 increasing perfluorooctanoate and perfluorooctane sulfonate contamination in human
 717 serum in Japan. *Chemosphere* 2007;66:293–301
- 718 • Haug LS, Thomsen C, Bechert G. Time trends and the influence of age and gender on
 719 serum concentrations of perfluorinated compounds in archived human samples. *Environ*
 720 *Sci Technol* 2009;43:2131–6
- 721 • Haug LS, Huber S, Schlabach M, Becher G, Thomsen C. Investigation on per- and
 722 polyfluorinated compounds in paired samples of house dust and indoor air from
 723 Norwegian homes. *Environ Sci Technol* 2011a;45:7991–7998
- 724 • Haug LS, Huber S, Becher G, Thomsen C. Characterisation of human exposure pathways
 725 to perfluorinated compounds comparing exposure estimates with biomarkers of exposure.
 726 *Environ Int* 2011b;37:687–693
- 727 • Herzke D, Huber S, Bervoets L, D'Hollander W, Hajslova J, Pulkrabova J, Brambilla G,
 728 De Filippis SP, Klenow S, Heinemeyer G, de Voogt P. Perfluorinated alkylated
 729 substances in vegetables collected in four European countries; occurrence and human
 730 exposure estimations. *Environ Sci Pollut Res* 2013;20:7930–7939

- 731 • Hites RA. Polybrominated diphenyl ethers in the environment and in people: A meta-
732 analysis of concentrations. *Environ Sci Technol* 2004;38:945–956
- 733 • Hölzer J, Midash O, Rauchfuss K, Kraft M, Reupert R, Angerer J, Kleeschulte P,
734 Marschall N, Wilhelm M. Biomonitoring of perfluorinated compounds in children and
735 adults exposed to perfluorooctanoate- contaminated drinking water. *Environ Health*
736 *Perspect* 2008;116:651–657
- 737 • Houde M, Czub G, Small JM, Backus S, Wang X, Alaee M, Muir DC. Fractionation and
738 bioaccumulation of perfluorooctane sulfonate (PFOS) isomers in a Lake Ontario food
739 web. *Environ Sci Technol* 2008;42:9397–9403
- 740 • Hühnerfuss H, Shah MH. Enantioselective chromatography—A powerful tool for the
741 discrimination of biotic and abiotic transformation processes of chiral environmental
742 pollutants. *J Chromatogr A* 2009;1216:481–502
- 743 • Inoue K, Okada F, Ito R, Kato S, Sasaki S, Nakajima AU, Uno A, Saijo Y, Sata F,
744 Yoshimura Y, Kishi R, Nakazawa H. Perfluorooctane sulfonate (PFOS) and related
745 perfluorinated compounds in human maternal and cord blood samples: assessment of
746 PFOS exposure in susceptible population during pregnancy. *Environ Health Perspect*
747 2004;112:1204–1207
- 748 • Jahnke A, Huberc S, Ternme C, Kylin H, Berger U. Development and application of a
749 simplified sampling method for volatile polyfluorinated alkyl substances in indoor and
750 environmental air. *J Chromatogr, A* 2007;1164(1–2):1–9
- 751 • Jin Y, Saito N, Harada KH, Inoue K, Koizumi A. Historical trends in human serum levels
752 of perfluorooctanoate and perfluorooctanesulphate in Shenyang. China Tohoku. *J Exp*
753 *Med* 2007;212:63–70
- 754 • Kadar H, Veyrand B, Barbarossa A, Pagliuca G, Legrand A, Bosher C, Boquien CY,
755 Durand S, Monteau F, Antignac JP, Le Bizec B. Development of an analytical strategy

based on liquid chromatography–high resolution mass spectrometry for measuring perfluorinated compounds in human breast milk: Application to the generation of preliminary data regarding perinatal exposure in France. *Chemosphere* 2011;85:473–480

- Kallenborn R, Hühnerfuss H. *Chiral Environmental Pollutants-Trace Analysis and Ecotoxicology*. Springer; 2001 edition. ISBN 978-3-662-06243-2

- Kannan K, Corsolini S, Falandysz J, Fillmann K, Kumar KS, Loganathan BG, Mohd MA, Olivero J, Van Wouwe N, Yang JH, Aldous KM. Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries. *Environ Sci Technol* 2004;38:4489–4495

- Kannan K, Tao L, Sinclair E, Pastva SD, Jude DJ, Giesy JP. Perfluorinated compounds in aquatic organisms at various trophic levels in a Great Lakes food chain. *Arch. Environ. Contam Toxicol* 2005;48 (4):559–566

- Kärman A, van Bavel B, Järnberg U, Hardell L, Lindström G. Perfluorinated chemicals in relation to other persistent organic pollutants in human blood. *Chemosphere* 2006a;64:1582–1591

- Kärman A, Mueller JF, van Bavel B, Harden F, Toms LM, Lindström G. Levels of 12 perfluorinated chemicals in pooled Australian serum, collected 2002–2003, in relation to age, gender, and region. *Environ Sci Technol* 2006b;40:3742–3748

- Kärman A, Ericson I, van Bavel B, Darnerud PO, Aune M, Glynn A, Lignell S, Lindström G. Exposure of perfluorinated chemicals through lactation: levels of matched human milk and serum and a temporal trend, 1996–2004, in Sweden. *Environ Health Perspect* 2007a;115:226–30

- Kärman A, Langlois I, van Bavel B, Lindström G, Oehme M. Identification and pattern of perfluorooctane sulfonate (PFOS) isomers in human serum and plasma. *Environ Int* 2007b;33(6):782–788

- 781 • Kärman A, Harada KH, Inoue K, Takasuga T, Ohi E, Koizumi A. Relationship between
782 dietary exposure and serum perfluorochemical (PFC) levels - A case study. *Environ Int*
783 2009;35:712–717
- 784 • Kärman A, Domingo JL, Llebaria X, Nadal M, Bigas E, van Bavel B, Lindström G.
785 Biomonitoring perfluorinated compounds in Catalonia, Spain: concentrations and trends
786 in human liver and milk samples. *Environ Sci Pollut Res Int* 2010;17(3):750–758
- 787 • Kato K, Calafat AM, Needham LL. Polyfluoroalkyl chemicals in house dust. *Environ Res*
788 2009;109:518–23
- 789 • Kato K, Wong LY, Jia LT, Kuklennyik Z, Calafat AM. Trends in exposure to
790 polyfluoroalkyl chemicals in the U.S. Population: 1999-2008. *Environ Sci Technol*
791 2011;45:8037–8045
- 792 • Kim SK, Kho YL, Shoeib M, Kim KS, Kim KR, Park JE, Shin YS. Occurrence of
793 perfluorooctanoate and perfluorooctanesulfonate in the Korean water system: Implication
794 to water intake exposure. *Environ Pollut* 2011a;159:1167-1173
- 795 • Kim SK, Lee KT, Kang CS, Tao L, Kannan K, Kim KR, Kim CK, Lee JS, Park PS, Yoo
796 YW, Ha JY, Shin YS, Lee JH. 2011b. Distribution of perfluorochemicals between sera
797 and milk from the same mothers and implications for prenatal and postnatal exposures.
798 *Environ Pollut* 2011b;159(1):169– 174
- 799 • Kissa E. *Fluorinated Surfactants and Repellents*, 2nd ed.; Marcel Dekker, Inc.: New York,
800 2001; Vol. 97, p 640
- 801 • Kubwabo C, Stewart B, Zhu J, Marro L. Occurrence of perfluorosulfonates and other
802 perfluorochemicals in dust from selected homes in the city of Ottawa, Canada. *J Environ*
803 *Monit* 2005;7:1074–8

- 804 • Kuklenyik Z, Reich JA, Tully LL, Needham LL, Calafat AM. Automated solid-phase
805 extraction and measurement of perfluorinated organic acids and amides in human serum
806 and milk. *Environ Sci Technol* 2004;38:3698–3704
- 807 • Lange FT, Wenz M, Schmidt CK, Brauch HJ. Occurrence of perfluoroalkyl sulfonates
808 and carboxylates in German drinking water sources compared to other countries. *Water*
809 *Sci Technol* 2007;56:151–158
- 810 • Lehmler HJ. Synthesis of environmentally relevant fluorinated surfactants—a review.
811 *Chemosphere* 2005;58:1471–1496
- 812 • Lehmler HJ, Harrad SJ, Hühnerfuss H, Kania-Korwel I, Lee CM, Lu Z, Wong CS. Chiral
813 polychlorinated biphenyl transport, metabolism, and distribution: A review. (2010)
814 *Environ Sci Technol* 2010;44 (8):2757-2766
- 815 • Lindstrom AB, Mark J, Strynar MJ, Libelo EL. Polyfluorinated Compounds: Past,
816 Present, and Future. *Environ Sci Technol* 2011;45:7954–7961
- 817 • Liu J, Li J, Zhao Y, Wang Y, Zhang L, Wu Y. The occurrence of perfluorinated alkyl
818 compounds in human milk from different regions of China. *Environ Int* 2010;36(5):433–
819 438
- 820 • Liu Y, Pereira AS, Beesoon S, Vestergren R, Berger U, Olsen GW, Glynn A, Martin JW.
821 Temporal trends of perfluorooctanesulfonate isomer and enantiomer patterns in archived
822 Swedish and American serum samples. *Environ Int* 2015;75:215-222
- 823 • Llorca M, Farre M, Pico Y, Teijon ML, Alvarez JG, Barcelo D. 2010. Infant exposure of
824 perfluorinated compounds: Levels in breast milk and commercial baby food. *Environ Int.*
825 2010;36(6):584–592
- 826 • Loos R, Wollgast J, Huber T, Hanke G. Polar herbicides, pharmaceutical products,
827 perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and nonylphenol and its

828 carboxylates and ethoxylates in surface and tap waters around Lake Maggiore in Northern
829 Italy. *Anal Bioanal Chem* 2007;387:1469–1478

830 • Loveless SE, Finlay C, Everds NE, Frame SR, Gillies PJ, O'Connor JC, Powley CR,
831 Kennedy GL. Comparative responses of rats and mice exposed to linear/branched, linear,
832 or branched ammonium perfluorooctanoate (APFO). *Toxicology* 2006;220:203–17

833 • Martin JW, Whittle DM, Muir DCG, Mabury SA. Perfluoroalkyl contaminants in a food
834 web from lake Ontario. *Environ Sci Technol* 2004;38 (20):5379–5385

835 • Martin JW, Asher BJ, Beesoon S, Benskin JP, Ross MS. PFOS or PreFOS? Are
836 perfluorooctane sulfonate precursors (PreFOS) important determinants of human and
837 environmental perfluorooctane sulfonate (PFOS) exposure? *J Environ Monit* 2010;12
838 11:1979–2004

839 • Midasch O, Schettgen T, Angerer J. Pilot study on PFOS and PFOA of the German
840 general population. *Int J Hyg Environ Health* 2006;209:489–496

841 • Midasch O, Drexler H, Hart N, Beckmann MW, Angerer J. Transplacental exposure of
842 neonates to perfluorooctanesulfonate and perfluorooctanoate: A pilot study. (2007) *Int*
843 *Arch Occup Environ Health* 2007;80(7):643-648

844 • Moriwaki H, Takatab Y, Arakawa R. Concentrations of perfluorooctane sulfonate (PFOS)
845 and perfluorooctanoic acid (PFOA) in vacuum cleaner dust collected in Japanese homes.
846 *J Environ Monit* 2003;5:753–757

847 • Mosch C, Kiranoglu M, Fromme H, Völkel W. Simultaneous quantitation of
848 perfluoroalkyl acids in human serum and breast milk using on-line sample preparation by
849 HPLC column switching coupled to ESI-MS/MS. *J Chromatogr B* 2010;878:2652–2658

850 • Nakata A, Katsumata T, Iwasaki Y, Ito R, Saito K, Izumi S, Makino T, Kishi R,
851 Nakazawa H, 2007. Measurement of perfluorinated compounds in human milk and house
852 dust. *Organohalogen Compd* 2007;69:2844–2846

- 853 • Nøst TH, Vestergren R, Berg V, Nieboer E, Odland JØ, Sandanger TM. Repeated
854 measurements of per- and polyfluoroalkyl substances (PFASs) from 1979 to 2007 in
855 males from Northern Norway: Assessing time trends, compound correlations and
856 relations to age/birth cohort. *Environ Int* 2014;67:43-53
- 857 • Olsen GW, Burris JM, Burlew MM, Mandel JH. Epidemiologic assessment of worker
858 serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations
859 and medical surveillance examinations. *J Occup Environ Med* 2003;45:260–70
- 860 • Olsen GW, Huang HY, Helzlsouer KJ, Hansen KJ, Butenhoff JL, Mandel JH. Historical
861 comparison of perfluorooctanesulfonate, perfluorooctanoate, and other fluorochemicals in
862 human blood. *Environ Health Perspect* 2005;113:539–45
- 863 • Olsen GW, Burris JM, Ehresman DJ, Froelich JW, Seacat AM, Butenhoff JL, Zobel LR.
864 Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and
865 perfluorooctanoate in retired fluorochemical production workers. *Environ Health Perspect*
866 2007a;115(9):1298–1305
- 867 • Olsen GW, Mair DC, Reagen WK, Ellefson ME, Ehresman DJ, Butenhoff JL, Zobel LR.
868 Preliminary evidence of a decline in perfluorooctanesulfonate (PFOS) and
869 perfluorooctanoate (PFOA) in American Red Cross blood donors. *Chemosphere*
870 2007b;68:105–111
- 871 • Olsen GW, Mair DC, Church TR, Ellefson ME, Reagen WK, Boyd TM, Herron RM,
872 Medhdizadehkashi Z, Nobiletti JB, Rios JA, Butenhoff JL, Zobel LR. Decline in
873 perfluorooctanesulfonate and other polyfluoroalkyl chemicals in American Red Cross
874 adult blood donors, 2000 - 2006. *Environ Sci Technol* 2008;42:4989–4995
- 875 • Olsen GW, Lange CC, Ellefson ME, Mair DC, Church TR, Goldberg CL, et al. Temporal
876 trends of perfluoroalkyl concentrations in American Red Cross adult blood donors, 2000–
877 2010. *Environ Sci Technol* 2012;46:6330–6338

- 878 • Paul AG, Jones KC, Sweetman AJ. A first global production, emission, and
879 environmental inventory for perfluorooctane sulfonate. *Environ Sci Technol*
880 2009;43(2):386–392
- 881 • Prevedouros K, Cousins IT, Buck RC, Korzeniowski SH. Sources, fate and transport of
882 perfluorocarboxylates. *Environ Sci Technol* 2006;40:32–44
- 883 • Renner R. The long and the short of perfluorinated replacements. *Environ Sci Technol*
884 2006;40:12–13
- 885 • Riddell N, Arsenault G, Benskin JP, Chitti B, Martin JW, McAlees A, McCrindle R.
886 Branched perfluorooctane sulfonate isomer quantification and characterization in blood
887 serum samples by HPLC/ESI-MS(/MS). *Environ Sci Technol* 2009;43(20):7902–7908
- 888 • Robson M, Harrad S. Chiral PCB signatures in air and soil: Implications for atmospheric
889 source apportionment. *Environ Sci Technol* 2004;38:1662–1666
- 890 • Roosens L, D'Hollander W, Bervoets L, Reynders H, Van Campenhout K, Cornelis C,
891 Van Den Heuvel R, Koppen G, Covaci A. (2010). Brominated flame retardants and
892 perfluorinated chemicals, two groups of persistent contaminants in Belgian human blood
893 and milk. *Environ Pollut* 2010;158:2546–2552
- 894 • Ross MS, Wong CS, Martin JW. Isomer-Specific Biotransformation of Perfluorooctane
895 Sulfonamide in Sprague–Dawley Rats. *Environ Sci Technol* 2012;46:3196–3203
- 896 • Saito N, Harada K, Inoue K, Sasaki K, Yoshinaga T, Koizumi A. Perfluorooctanoate and
897 perfluorooctane sulfonate concentrations in surface water in Japan. *J Occup Health*
898 2004;46:49–59
- 899 • Sakr CJ, Leonard RC, Kreckmann KH, Slade MD, Cullen MR. Longitudinal study of
900 serum lipids and liver enzymes in workers with occupational exposure to ammonium
901 perfluorooctanoate. *J Occup Environ Med* 2007;49(8):872–879

- 902 • Scheringer M, Vögl T, von Grote J, Capaul B, Schubert R, Hungerbühler K. (2001).
 903 Scenario-based risk assessment of multi-use chemicals: Application to solvents. Risk
 904 Anal 2001;21(3):481–497
- 905 • Schultz M, Barofsky D, Field J. Fluorinated Alkyl Surfactants. Environ Eng Sci.
 906 2003;20(5):487-501
- 907 • Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Eldridge SR, Elcombe CR, Butenhoff
 908 JL. Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats.
 909 Toxicology 2003;183:117–31
- 910 • Sharpe RL, Benskin JP, Laarman AH, MacLeod SL, Martin JW, Wong CS, Goss GG.
 911 Perfluorooctane sulfonate toxicity, isomer-specific accumulation, and maternal transfer in
 912 zebrafish (*Danio rerio*) and rainbow trout (*Oncorhynchus mykiss*). Environ Toxicol Chem
 913 2010;29(9):1957–1966
- 914 • Shoeib M, Harner T, Wilford BH, Jones KC, Zhu JP. Perfluorinated sulfonamides in
 915 indoor and outdoor air and indoor dust: Occurrence, partitioning, and human exposure.
 916 Environ Sci Technol 2005;39(17):6599–6606
- 917 • Shoeib M, Harner T, Webster GM, Lee SC. Indoor sources of poly- and perfluorinated
 918 compounds (PFCs) in Vancouver, Canada: implications for human exposure. Environ Sci
 919 Technol 2011;45:7999–8005
- 920 • Skutlarek D, Exner M, Färber H. Perfluorinated Surfactants in Surface and Drinking
 921 Waters. Environ Sci Pollut Res 2006;13(5):299–307
- 922 • So MK, Yamashita N, Taniyasu S, Jiang Q, Giesy JP, Chen K, Lam PKS. Health risks in
 923 infants associated with exposure to perfluorinated compounds in human breast milk from
 924 Zhoushan. China. Environ Sci Technol 2006;40(9):2924–2929

- 925 • Sonne C. Health effects from long-range transported contaminants in Arctic top
 926 predators: an integrated review based on studies of polar bears and relevant model
 927 species. *Environ Int* 2010;36:461–491
- 928 • Steenland K, Fletcher T, Savitz DA. Epidemiologic evidence on the health effects of
 929 perfluorooctanoic acid (PFOA). *Environ Health Perspect* 2010;118(8):1100–1108
- 930 • Strynar MJ, Lindstrom AB. Perfluorinated compounds in house dust from Ohio and North
 931 Carolina, USA. *Environ Sci Technol* 2008;42:3751–6
- 932 • Sundström M, Ehresman DJ, Bignert A, Butenhoff JL, Olsen GW, Chang SC, Bergman
 933 A. A temporal trend study (1972–2008) of perfluorooctanesulfonate,
 934 perfluorohexanesulfonate, and perfluorooctanoate in pooled human milk samples from
 935 Stockholm, Sweden. *Environ Int* 2011;37:178–183
- 936 • Takagi S, Adachi F, Miyano K, Koizumi Y, Tanaka H, Mimura M, Watanabe I, Tanabe
 937 S, Kannan K. Perfluorooctanesulfonate and perfluorooctanoate in raw and treated tap
 938 water from Osaka, Japan. *Chemosphere* 2008;72:1409–1412
- 939 • Tanaka S, Fujii S, Lien NPH, Nozoe M, Chinagarn K, Kimura K, Shivakoti B, Anton A,
 940 Maketab M, Wirojanagud W, Hu JY, Kitpati S, Shimizu J, Tittlemier S, Lindström G,
 941 Saito N. Contamination of perfluorinated compounds in water environment of Asian
 942 countries. *Organohalogen Compd* 2008;70:402–405
- 943 • Taniyasu S, Kannan K, Horii Y, Hanari N, Yamashita N. A survey of perfluorooctane
 944 sulfonate and related perfluorinated organic compounds in water, fish, birds, and humans
 945 from Japan. *Environ Sci Technol* 2003;37:2634–2639
- 946 • Tao L, Ma J, Kunisue T, Libelo EL, Tanabe S, Kannan K. Perfluorinated compounds in
 947 human breast milk from several Asian countries, and in infant formula and dairy milk
 948 from the United States. *Environ Sci Technol* 2008;42(22):8597–8602

- 949 • Taves DR. Determination of submicromolar concentrations of fluoride in biological
950 samples. *Talanta* 1968;15:1015-1023
- 951 • Thomsen C, Haug L, Stigum H, Frøshaug M, Broadwell SL, Becher G. Changes in
952 Concentrations of Perfluorinated Compounds, Polybrominated Diphenyl Ethers, and
953 Polychlorinated Biphenyls in Norwegian Breast-Milk during Twelve Months of
954 Lactation. *Enviro. Sci Technol* 2010;44:9550–9556
- 955 • Tittlemier SA, Pepper K, Edwards L. Concentrations of perfluorooctanesulfonamides in
956 Canadian total diet study composite food samples collected between 1992 and 2004. *J*
957 *Agric Food Chem* 2006;54:8385–8389
- 958 • Tomy GT, Tittlemier SA, Palace VP, Budakowski WR, Braekevelt E, Brinkworth L,
959 Freisen K. Biotransformation of N-ethyl perfluorooctanesulfonamide by rainbow trout
960 (*Onchorhynchus mykiss*) liver microsomes. *Environ Sci Technol* 2004;38:758–762
- 961 • Trudel D, Horowitz L, Wormuth M, Scheringer M, Cousins IT, Hungerbuhler K.
962 Estimating consumer exposure to PFOS and PFOA. *Risk Anal* 2008;28:251–269
- 963 • Ullah S, Hube S, Bignert A, Berger U. Temporal trends of perfluoroalkane sulfonic acids
964 and their sulfonamide-based precursors in herring from the Swedish west coast 1991–
965 2011 including isomer-specific considerations. *Environ Int* 2014;65: 63–72
- 966 • UNEP, United Nations Environmental Programme. The 9 New POPs: An Introduction to
967 the Nine Chemicals Added to the Stockholm Convention by the Conference of the Parties
968 at its Fourth Meeting, 2010
- 969 ○ www.pops.int/
- 970 • USEPA. Provisional Health Advisories for Perfluorooctanoic Acid (PFOA) and
971 Perfluorooctane Sulfonate (PFOS); U.S. Environmental Protection Agency: Washington,
972 DC, January 8, 2009. Accessed September 2014

- 973 ○ [http://www.epa.gov/opptintr/pfoa/pubs/Final%20PFOA%20PFOS%20RfD%20m](http://www.epa.gov/opptintr/pfoa/pubs/Final%20PFOA%20PFOS%20RfD%20memo%2010-28-09.pdf)
 974 [emo%2010-28-09.pdf](http://www.epa.gov/opptintr/pfoa/pubs/Final%20PFOA%20PFOS%20RfD%20memo%2010-28-09.pdf)
- 975 • USEPA 2010/15 PFOA Stewardship Program. Accessed September 2014
- 976 ○ <http://www.epa.gov/oppt/pfoa/pubs/stewardship/index.htm>
- 977 • Vestergren R, Cousins IT, Trudel D, Wormuth M, Scheringer M. Estimating the
 978 contribution of precursor compounds in consumer exposure to PFOS and PFOA.
 979 Chemosphere 2008;73:1617–1624
- 980 • Völkel W, Genzel-Boroviczeny O, Demmelmair H, Gebauer C, Koletzko B, Twardella D,
 981 Raab U, Fromme H. 2008. Perfluorooctane sulphonate (PFOS) and perfluorooctanoic
 982 acid (PFOA) in human breast milk: results of a pilot study. Int J Hyg Environ Health
 983 2008;211(3–4):440–446
- 984 • Wang Y, Yeung LWY, Taniyasu S, Yamashita N, Lam JCW, Lam PKS. Perfluorooctane
 985 Sulfonate and Other Fluorochemicals in Waterbird Eggs from South China. Environ Sci
 986 Technol 2008;42:8146–8151
- 987 • Wang Y, Arsenault G, Riddell N, McCrindle R, McAlees A, Martin JW. Perfluorooctane
 988 sulfonate (PFOS) precursors can be metabolized enantioselectively: Principle for a new
 989 PFOS source tracking tool. Environ Sci Technol 2009;43(21):8283–8289
- 990 • Wang Y, Beesoon S, Benskin JP, De Silva AO, Genuis SJ, Martin JW. Enantiomer
 991 fractions of chiral perfluorooctanesulfonate (PFOS) in human sera. Environ Sci Technol
 992 2011;45(20):8907–8914
- 993 • Wilhelm M, Angerer J, Fromme H, Hölzer J. Contribution to the evaluation of reference
 994 values for PFOA and PFOS in plasma of children and adults from Germany. Int J Hyg
 995 Environ Health 2009;212:56–60
- 996 • Xie W, Wu Q, Kania-Korwel I, Tharappel JC, Telu S, Coleman MC, Glauert HP, Kannan
 997 K, Mariappam SVS, Spitz D, Weydert J, Lehmler HJ. Subacute exposure to N-ethyl

998 perfluorooctanesulfonamido ethanol results in the formation of perfluorooctanesulfonate
 999 and alters superoxide dismutase activity in female rats. Arch Toxicol 2009;83:909–924

1000 • Xu L, Krenitsky DM, Seacat AM, Butenhoff JL, Anders MW. Biotransformation of N-
 1001 ethyl-N-(2-hydroxyethyl)perfluorooctanesulfonamide by rat liver microsomes, cytosol,
 1002 and slices and by expressed rat and human cytochromes P450. Chem Res Toxicol
 1003 2004;17:767–775

1004 • Yeung LW, So MK, Jiang G, Taniyasu S, Yamashita N, Song M, Wu Y, Li J, Giesy JP,
 1005 Guruge KS, Lam PKS. 2006. Perfluorooctanesulfonate and related perfluorochemicals in
 1006 human blood samples from China. Environ Sci Technol 2006;40:715–720

1007 • Zhang Y, Beesoon S, Zhu L, Martin JW. Isomers of perfluorooctanesulfonate and
 1008 perfluorooctanoate and total perfluoroalkyl acids in human serum from two cities in
 1009 North China. Environ Int 2013;53:9–17

1010 • Zhao YG, Wong CKC, Wong MH. Environmental contamination, human exposure and
 1011 body loadings of perfluorooctane sulfonate (PFOS), focusing on Asian countries.
 1012 Chemosphere 2012;89:355–368

1013 • Zushi Y, Hogarth JN, Masunaga S. Progress and perspective of perfluorinated compound
 1014 risk assessment and management in various countries and institutes. Clean Techn Environ
 1015 Policy 2012;14:9–20

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Table 1. Comparison of reported PFOS concentrations and ranges in human blood or serum (ng/mL)

Authors	Year	Country	Matrix	n	% DF	Mean	Median ^c	Range
Ericson et al.	2007	Spain	Whole blood	48	100	7.64	7.6	0.76-16.2
Fromme et al. (b)	2007	Germany	Plasma	356	100	13.5	13.7	2.1-55.0
Hansen et al.	2001	USA	Serum	65	100	25.519	25.7	6.7-81.5
Haug et al. (b)	2011	Norway	Serum	41	100	6.9	NR	2.3-15.0
Hölzer et al.	2008	North Rhine	Plasma	80	NR	NR	4.3	1.5-26.2
Jin et al.	2007	China	Serum	119	NR	NR	22.4	0.2-145.0
Kannan et al.	2004	USA	Serum	46/29 ^d	91/93 ^d	32.5/32.9 ^d	28.9/26.2 ^d	<1.3-124
		USA	Whole blood	11/19 ^d	100/100 ^d	66/73.2 ^d	81/72 ^d	11-164
		USA	Plasma	70	100	42.8	42	16-83
		Colombia	Whole blood	25/31 ^d	100/100 ^d	8.0/8.5 ^d	7.3/8.1 ^d	4.6-14
		Brazil	Whole blood	17/10 ^d	100/100 ^d	10.7/13.5 ^d	8.4/12.7 ^d	4.3-35
		Italy	Serum	8/42 ^d	87.5/90.5 ^d	4.4/4.3 ^d	3.5/4.2 ^d	<1-10.3
		Poland	Whole blood	15/10 ^d	100/100 ^d	33.3/55.4 ^d	33.8/40.9 ^d	16.0-116
		Belgium	Plasma	4/16 ^d	100/100 ^d	11.1/16.8 ^d	10.4/17.6 ^d	4.5-27.0
		India	Serum	11/34 ^d	55/50 ^d	2.3/1.7 ^d	2.5/1.3 ^d	<1-3
		Malaysia	Whole blood	7/16 ^d	100/100 ^d	11.7/13.2 ^d	12.7/13.1 ^d	6.2-18.8
		Korea	Whole blood	25/25 ^d	100/100 ^d	15.1/27.1 ^d	11.3/18.3 ^d	3.0-92

		Japan	Serum	13/25 ^d	100/100 ^d	20.1/14.1 ^d	18.3/12.4 ^d	4.1-40.3
Kärrman et al. (a)	2006	Sweden	Whole blood	66	100	16	17.1	1.7-37.0
Kärrman et al. (b)	2006	Australia	Serum	40	NR	21.3	20.8	12.7-29.5
Kärrman et al. (a)	2007	Sweden	Serum	12	100	20.7	18.7	8.2-48.0
Kato et al.	2011	USA	Serum (years 99-00)	1562	100	30.4	NR	NR
(NHANES reports			Serum (years 03-04)	2094	99.9	20.7	NR	NR
overview). Calafat et			Serum (years 05-06)	2120	99.9	17.1	NR	NR
al. (2007) (a) (b)			Serum (years 07-08)	2100	99.8	13.2	NR	NR
Midash et al.	2006	Germany	Plasma	105	100	NR	22.3	6.2-131.0
Olsen et al.	2005	USA	Serum	178	NR	30.1	29.5	NR
			Plasma	178	NR	33.3	34.7	NR
Yeung et al.	2006	China	Serum	85	NR	NR	52.7	NR

c) For concentrations <LOQ, the value was assumed to = 1/2 LOQ. d) Separate female/male data reported for this study.

DF: Detection frequency. NR: Not reported.

Table 2. Comparison of reported PFOS concentrations and ranges in human breast milk (ng/mL)

Authors	Year	Country	n	% DF	Mean	Median^c	Range
Antignac et al.	2013	France	48	90	0.092	0.075	<0.050-0.330
Bernsmann and Fürst	2008	Germany	203	66	NR	0.082	0.05-0.284
Fromme et al.	2010	Germany	201	72	NR	0.040	<0.030-0.110
Guerranti et al.	2013	Italy	49	41	0.85	NR	<1.020-4.280
Haug et al. (b)	2011	Norway	19	100	0.093	0.087	0.004-0.250
Kadar et al.	2011	France	30	100	NR	0.074	0.024-0.171
Kärrman et al. (a)	2007	Sweden	12	100	0.201	0.121	0.063-0.465
Kärrman et al.	2010	Spain	10	100	0.12	0.110	0.070-0.220
Kim et al. (b)	2011	Korea	17	100	0.061	NR	0.032-0.130
Liu et al.	2010	China	24	100	0.046	0.049	0.006-0.137
Llorca et al.	2010	Spain	20	95	0.071	0.084	0.028-0.865
Mosch et al.	2010	Germany	20	95	NR	0.049	<0.030-0.195
Nakata et al.	2007	Japan	51	100	NR	NR	0.008-0.401
Roosens et al.	2010	Belgium	22	NR	NR	2.900	<0.400-28.2
So et al.	2006	China	19	100	0.105	0.100	0.045-0.360
Sundstrom et al.	2011	Sweden	20 ^d	100	0.156	0.206	0.088-0.151

Tao et al.	2008	USA	45	96	NR	0.106	<0.032-0.617
		Cambodia	24	100	0.067	0.040	0.017-0.327
		Vietnam	40	100	0.076	0.058	0.017-0.393
		Indonesia	20	100	0.084	0.067	0.025-0.256
		Philippines	24	100	0.098	0.104	0.027-0.208
		Malaysia	13	100	0.121	0.111	0.049-0.350
		India	39	85	0.046	0.039	<0.011-0.120
		Japan	24	100	0.232	0.196	0.140-0.523
Thomsen et al.	2010	Norway	68	NR	NR	0.110	0.028-0.36
Völkel et al.	2008	Germany	19	100	0.116	0.113	0.028-0.239
		Germany	38	100	0.126	0.123	0.033-0.309
		Hungary	13	100	0.317	0.330	0.096-0.639

c) For concentrations <LOQ, the value was assumed = 1/2 LOQ. d) 20 pools of human milk.

DF: Detection frequency. NR: Not reported.

Table 3. Comparison of reported PFOS concentrations and ranges (ng/L) in drinking water

Authors	Year	Country	n	% DF	A/GM	Median ^c	Range
Ericson et al.	2008	Spain	4	100	0.57 ^c (GM)	0.59	0.39-0.87
Ericson et al.	2009	Spain	40	87	3.72 (GM)	0.51	<0.12-58.12
Kim et al.(a)	2011	Korea	15	NR	NR	NR	<0.33-11.00
Loos et al.	2007	Italy	6	100	8.1 (A)	NR	6.20-9.70
Saito et al.	2004	Japan	30	67	0.7-12.5 ^d (GM)	0.65	<0.10-12.00
Skutlarek et al.	2006	Germany	37	35	2.09 ^c (GM)	1.00	<1.00-22.00
Takagi et al.	2008	Japan	26	96	1.51 (GM)	1.90	<0.16-22.00
Tanaka et al.	2008	Japan	NR	NR	NR	NR	<0.01-143.0

c) For concentrations <LOQ, the value was assumed = 1/2 LOQ. b) Estimated in 6 different areas.

DF: Detection frequency. A: Average. GM: Geometric mean. NR: Not reported.

Table 4. Comparison of reported PFOS concentrations and ranges in indoor dust (ng/g)

Authors	Year	Country/Microenvironment	Source	n	% DF	Average	Median ^c	Range
		Category						
Bjorklund et al.	2009	Sweden / Houses	Dust	10	100	49.0 ^d	39.0	15-120
		Sweden / Apartments	Dust	38	79	175.0 ^d	85.0	<8.0-1100
		Sweden / Offices	Dust	10	100	144.0 ^d	110.0	29-490
		Sweden / Daycare centres	Dust	10	100	38.0 ^d	31.0	23-65
		Sweden / Cars	Dust	5	60	18.0 ^d	12.0	<8.0-33
Ericson Jogsten et al.	2012	Spain / Houses	Dust	10	100	2.1	2.2	0.13-12.0
Goosey and Harrad	2011	UK / Cars	Dust	20	100	132.0	97.0	20-1500
		UK / Classrooms	Dust	42	100	640.7	980.0	22-3700
		UK / Houses	Dust	45	100	144.7	450.0	3.5-7400
		UK / Offices	Dust	20	100	182.5	370.0	20-1000
		Australia / Houses	Dust	20	100	187.0	170.0	6.5-8100
		Canada / Houses	Dust	19	100	157.8	140.0	42-1300
		France / Houses	Dust	10	100	193.8	160.0	54-1700
		Germany / Houses	Dust	10	100	188.9	170.0	47-1000
		Kazakhstan / Houses	Dust	9	80	12.5	59.0	<0.03-130

		Thailand / Houses	Dust	20	100	19.5	16.0	3-130
		USA / Houses	Dust	10	100	318.1	310.0	110-930
Kato et al.	2009	Australia / Houses	Dust	39	74	NR	480.0	<2.6-18000
Kubwabo et al.	2005	Canada / Houses	Dust	67	67	443.7	37.8	2.3-5065
Moriwaki et al.	2003	Japan / Houses	Dust	16	100	39.5	25.0	15.0-2500
Strynar et al.	2008	USA / Houses (102) and child daycare centres (10)	Dust	112	95	761.0	201.0	<8.9-12100

c) For concentrations <LOQ, the value was assumed = 1/2 LOQ d) Arithmetic mean.

DF: Detection frequency. NR: Not reported.

Table 5. Comparison of reported PFOS concentrations and ranges in indoor and outdoor air (pg/m³)

Authors	Year	Country	Source	n	% DF	Mean	Median ^c	Range
Barber et al.	2007	Norway	Indoor air	4	0	NR	NR	<47.4
Ericson Jogsten et al.	2012	Spain	Indoor air	10	33	0.3	0.1	<0.13-67.0
Goosey and Harrad	2012	UK	Indoor air	20	90	12.4	11.5	<1.0-400.0
		UK	Indoor air	12	100	49.4	55.0	12.0-89.0
Shoeib et al.	2011	Canada	Indoor air	39	0	<LOD	<LOD	<LOD
Barber et al.	2007	UK	Outdoor air	2	NR	NR	NR	46
		UK	Outdoor air	10	NR	NR	NR	1.6
Dreyer et al.	2009	Germany	Outdoor air	117	0	<LOD	<LOD	<LOD
		Germany	Outdoor air	121	0	<LOD	<LOD	<LOD
Genualdi et al.	2010	Diff. Countries	Outdoor air	20	50	NR	NR	2.03-149.5
Goosey and Harrad	2012	UK	Outdoor air	10	70	1.5	1.6	<0.1-6.1
Shoeib et al.	2011	Canada	Outdoor air	6	0	<LOD	<LOD	<LOD

c) For concentrations <LOQ, the value was assumed = 1/2 LOQ.

DF: Detection frequency. NR: Not reported.

Table 6. List of PFOS, its salts and its main precursors

CAS number	Common name	Systematic name	Molecular formula
N/A	PFOS anion	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonate	$C_8F_{17}SO_3^-$
	PFOS acid		
1763-23-1	(perfluorooctanesulfonic acid)	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid	$C_8F_{17}SO_3H$
2795-39-3	PFOS potassium (K^+) salt	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid, potassium salt	$C_8F_{17}SO_3K$
29081-56-9	PFOS ammonium (NH_4^+) salt	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid, ammonium salt	$C_8F_{17}SO_3NH_4$
29457-72-5	PFOS lithium (Li^+) salt	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid, lithium salt	$C_8F_{17}SO_3Li$
70225-14-8	PFOS diethanolamine (DEA) salt	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid, compd. with 2,2-iminobis[ethanol] (1:1)	$C_8F_{17}SO_3NH(CH_2CH_2OH)_2$
307-35-7	POSF	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonyl fluoride	$C_8F_{18}O_2S$
1691-99-2	N-EtFOSE alcohol	N-ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-(2-hydroxyethyl)-1-Octanesulfonamide	$C_{12}H_{10}F_{17}NO_3S$

4151-50-2	N-EtFOSA	N-ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonamide	$C_{10}H_6F_{17}NO_2S$
24448-09-7	N-MeFOSE alcohol	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-(2-hydroxyethyl)-N-methyl-1-Octanesulfonamide	$C_{11}H_8F_{17}NO_3S$
31506-32-8	N-MeFOSA	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-methyl-1-Octanesulfonamide	$C_9H_4F_{17}NO_2S$
25268-77-3	N-MeFOSEA	2-Propenoic acid, 2-[[heptadecafluorooctyl)sulfonyl]methylamino]ethyl ester	$C_{14}H_{10}F_{17}NO_4S$
423-82-5	N-EtFOSEA	2-Propenoic acid, 2-[ethyl[(heptadecafluorooctyl)sulfonyl]amino]ethyl ester	$C_{15}H_{12}F_{17}NO_4S$

Table 7. Linear versus branched chain composition profiles and enantiomer fractions (EFs) of PFOS and its precursors in various matrices

Authors	Year	Country	Study	Matrix	n	Analytes
Asher et al.	2012	Canada	Lake	Aquatic Species	67	PFOSA (\approx 57% linear)
						PFOS (>90% linear)
				Water	2	PFOS (70% linear)
				Sediment	3	PFOS (>90% linear)
Beesoon et al.	2011	Canada	Human	Dust	18	PFOS (\approx 70% linear)
				Serum	20	PFOS (\approx 64% linear)
				Cord serum	20	PFOS (\approx 54% linear)
Benskin et al.	2007	Canada	Human	Serum	14	PFOS (\approx 80% linear)
Haug et al.	2009	Norway	Human	Serum	57	PFOS (53-78 linear)
Houde et al.	2008	Canada	Niagara/Lake	Fish	22	PFOS (88-93% linear)
				Water	NR	PFOS (43-56 linear)
Kärman et al. (b)	2007	Sweden	Human	Serum/blood	17	PFOS (68% linear)
		UK			13	PFOS (59% linear)
		Australia			40	PFOS (59% linear)
Ross et al.	2012	Canada	Animals	Blood	8	PFOSA (\approx 78% linear)
				Blood	8	PFOS (\approx 77% linear)

				Heart	8	PFOSA (≈93% linear)
				Fat	8	PFOSA (≈86% linear)
Sharpe et al.	2010	Canada	-	Fish	NR	PFOS (>70% linear)
Wang et al.	2011	Canada	Animals	Rats	3	1m-PFOS (EF≈0.5)
			Human	Serum	8	1m-PFOS (EF=0.43)
			Human	Serum	7	1m-PFOS (EF=0.35-0.43)
Zhang et al.	2013	China	Human	Serum	129	PFOS (48% linear)

NR: Not reported.

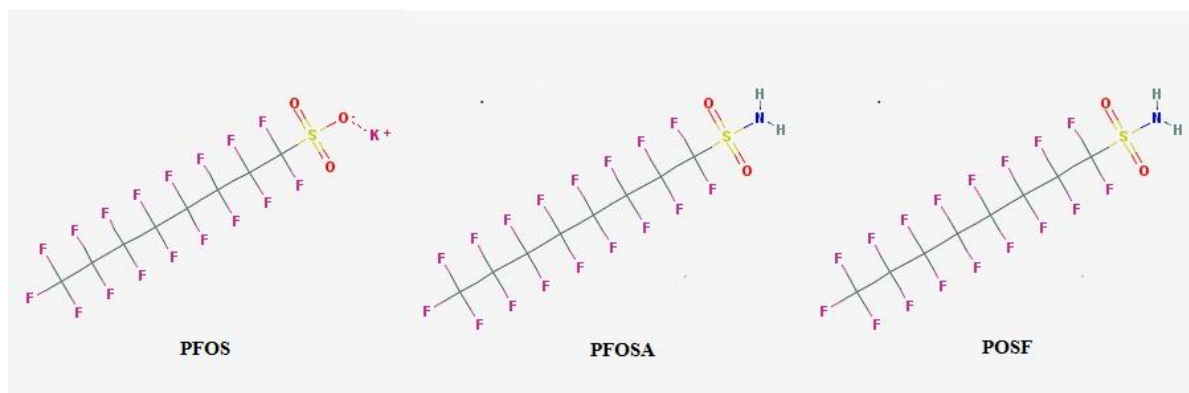


Fig. 1. PFOS K salt, PFOSA, and POSF structures

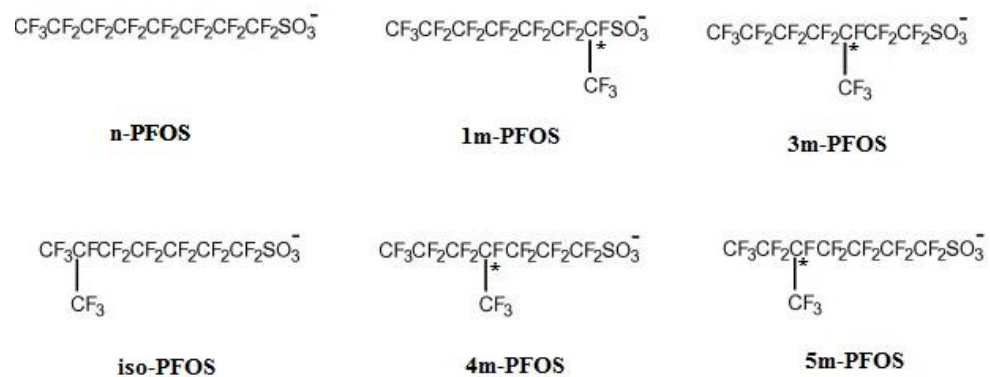


Fig 2. Linear PFOS structure (named as n-PFOS) and monomethylated PFOS branched isomers, where the chiral carbon is represented by *. Each isomer containing a chiral centre has 2 enantiomers (R and S)